UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

IN RE NUVARING® PRODUCTS LIABILITY LITIGATION	)	Case No. 4:08-MD-1964 RWS
	)	ALL CASES

MEMORANDUM AND ORDER

Defendants ("Organon") have moved to exclude the testimony of Plaintiffs' proffered multi-district litigation ("MDL") expert, Shelly Ann Tischkau, Ph.D. Organon asks me to find, as a matter of law, that Dr. Tischkau is unqualified as an expert and that her opinions are so unreliable that they should be excluded from being tested by any cross-examination at trial, being weighed by any jury, or even limited in any respect by any trial judge. Because I find that Dr. Tischkau is qualified to render her opinions in this matter and that she uses sufficiently reliable methodology, I will deny Organon's motion.

I. BACKGROUND

This MDL relates to the manufacture, marketing, and sale of the prescription pharmaceutical known as NuvaRing. NuvaRing, which is manufactured, marketed, and sold by Organon, is a member of a class of prescription drugs known as combined hormonal contraceptives ("CHCs"). Unlike oral CHCs, NuvaRing takes the form of a flexible ring which releases hormones over the course of treatment. The ring is vaginally inserted by women for birth control. Each month, the ring is removed and a new ring is inserted.

CHCs contain an estrogen, typically ethinyl estradiol ("EE"), and a progestin. The "generation" of CHC depends upon the type of progestin. Each "generation" of CHC typically contains the following progestins: first-generation contains norethynodrel; second-generation contains levonorgestrel; and third-generation CHCs contain desogestrel, gestodene, or

norgestimate. NuvaRing uses the active metabolite of desogestrel, etonogestrel, and is therefore considered a third-generation progestin.

Plaintiffs claim that etonogestrel has been linked to an undisclosed increased risk of venous thromboembolism, including deep vein thrombosis and pulmonary embolism.[1] Plaintiffs allege they have been injured by the use of NuvaRing and have asserted the following claims: strict products liability for defective manufacturing, defective design, failure to test, and inadequate warnings; breach of express / implied warranties; and negligence.

In support of these claims, Plaintiffs proffer Dr. Tischkau as an expert in pharmacology. Organon disputes the qualifications of Dr. Tischkau and the reliability of the methodology underlying her opinions.

II. LEGAL STANDARD

Federal Rule of Evidence 702 and Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993), govern the admissibility of expert testimony. The Daubert standard applies to all expert testimony, whether based on scientific competence or other specialized or technical expertise. See Polski v. Quigley Corp., 538 F.3d 836, 838 (8th Cir. 2008). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

"[I]t is the responsibility of the trial judge to determine whether a particular expert has sufficient specialized knowledge to assist jurors in deciding the specific issues in the case."

[1] Venous thromboembolism is a blood clot that forms within a vein. Deep vein thrombosis is a blood clot that forms in a vein not externally visible, typically in the veins of the lower extremities. A pulmonary embolism forms when part or all of a blood clot breaks free and lodges in one of the lungs. These conditions have varying severity and can be life threatening.

Wheeling Pittsburgh Steel Corp. v. Beelman River Terminals, Inc., 254 F.3d 706, 715 (8th Cir. 2001). "Once initial expert qualifications and usefulness to the jury are established, however, a district court must continue to perform its gatekeeping role by ensuring that the actual testimony does not exceed the scope of the expert's expertise, which if not done can render expert testimony unreliable . . . ." Id.

"When faced with a proffer of expert scientific testimony, the trial court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'" Polski, 538 F.3d at 838 (quoting Daubert, 509 U.S. at 592–93). Thus, under Rule 702, the trial judge also acts as a gatekeeper by screening evidence for relevance and reliability. Daubert, 509 U.S. at 589.

Thus, the district court applies a three-part test when screening expert testimony under Rule 702:

> First, evidence based on scientific, technical, or other specialized knowledge must be useful to the finder of fact in deciding the ultimate issue of fact. This is the basic rule of relevancy. Second, the proposed witness must be qualified to assist the finder of fact. Third, the proposed evidence must be reliable or trustworthy in an evidentiary sense, so that, if the finder of fact accepts it as true, it provides the assistance the finder of fact requires.

Polski, 538 F.3d at 839 (quoting Lauzon v. Senco Prods., Inc., 270 F.3d 681, 686 (8th Cir. 2001)).

"Rule 702 reflects an attempt to liberalize the rules governing the admission of expert testimony. The rule clearly is one of admissibility rather than exclusion." Lauzon, 270 F.3d at 686 (internal quotations and citations omitted). "The exclusion of an expert's opinion is proper only if it is so fundamentally unsupported that it can offer no assistance to the jury." Wood v.

Minn. Mining & Mfg. Co., 112 F.3d 306, 309 (8th Cir. 1997) (internal quotations and citation omitted).

When assessing the reliability of expert testimony, a trial court should consider several factors, including: "(1) whether the concept has been tested, (2) whether the concept has been subject to peer review, (3) what the known rate of error is, and (4) whether the concept is generally accepted by the community." Miller v. Baker Implement Co., 439 F.3d 407, 412 (8th Cir. 2006) (citing Daubert, 509 U.S. at 593–95). There is no requirement that courts rely on each factor, as the gatekeeping inquiry is flexible and must be "tied to the facts" of the particular case. Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 150 (1999) (quoting Daubert, 509 U.S. at 591).

"[T]he rejection of expert testimony is the exception rather than the rule." Robinson v. GEICO General Ins. Co., 447 F.3d 1096, 1100 (8th Cir. 2006) (citing Fed. R. Evid. 702 advisory comm. note). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 595.

III. ARGUMENT AND ANALYSIS

Plaintiffs intend to call Dr. Tischkau at trial to testify, based on her expertise, research, and review of epidemiologic and scientific literature, that NuvaRing produces a risk of VTE that is greater than the risk presented by hormonal contraceptives containing second-generation progestins. Plaintiffs list four opinions of Dr. Tischkau that they defend here: 1) NuvaRing Clinical Trial 34218 reported variability in terms of the amount of EE delivered to the bloodstream; 2) the NuvaRing label contains misrepresentations, including the pharmacokinetics portion of the label showing that NuvaRing delivers a low dose of EE at a steady state; 3) the

pharmacokinetic data of NuvaRing supports the epidemiology literature concluding that NuvaRing is associated with an increased risk of VTE in comparison to hormonal contraceptives containing second-generation progestins; and 4) the NuvaRing label fails to adequately warn physicians and patients of the increased VTE risk associated with NuvaRing.

Dr. Tischkau was asked by Plaintiffs to review the pharmacokinetic and pharmacodynamic properties associated with the use of NuvaRing. Dr. Tischkau also reviewed scientific and medical literature stating: increasing levels of estrogenicity are associated with increased risk of VTE; the androgenic properties of progestins reduce overall estrogenicity; the prothombotic effects of estrogen are inhibited by progestins; the estrogenicity of a given estrogen/progestin combined contraceptive may be predicted by the effects on sex hormone binding globulin (SHBG); SHBG correlates with risk for VTE; and NuvaRing use results in higher SHBG levels than contraceptives containing second-generation progestins.

Dr. Tischkau found that a NuvaRing clinical trial revealed that the pharmacokinetic properties of the hormones resulted in a slower rise in progestin concentration levels as compared to estrogen levels. She found that the resulting estrogenicity of NuvaRing may vary over the course of therapy. Additionally, Dr. Tischkau pointed to evidence that the serum level of EE, the form of estrogen present in NuvaRing, rapidly rose in a "burst" effect at varying times during NuvaRing use in clinical trials. This resulted in periods of time during which the estrogen was unopposed by progestin, exposing NuvaRing users to an increased risk of VTE. Dr. Tischkau opined that the NuvaRing labeling does not accurately and completely reflect the data from clinical trials and is therefore misleading to doctors and patients.

A. Qualifications

1. Objections and Response

Organon objects to the admission of Dr. Tischkau's testimony because, they argue, she is not qualified as an expert in human pharmacokinetics or in thrombosis, VTEs, or hematology.

First, Organon argues that because Dr. Tischkau's research involves primarily animal studies, she is not qualified to testify as to human pharmacokinetics. Plaintiffs respond that Dr. Tischkau has a Ph.D. in physiology with formal training in reproductive pharmacology, reproductive endocrinology, and reproductive biology. Moreover, Dr. Tischkau is an Assistant Professor in the Southern Illinois University School of Medicine's Department of Pharmacology, where she holds the position of Director of the Endocrine-Reproduction-Gastrointestinal unit. At the School of Pharmacology, Dr. Tischkau lectures on principles of pharmacology, female reproductive pharmacology, reproductive toxicology, and serves as the course coordinator for advanced neuropharmacology.

Organon also argues that because Dr. Tischkau did not claim expertise in hematology, VTEs, or thrombosis, she should be precluded from testifying that NuvaRing presents greater risks of VTE and thrombosis than oral contraceptives or hormonal contraceptives using a second-generation progestin. Plaintiffs respond that Dr. Tischkau need not have expertise in those specific fields because Dr. Tischkau intends to apply the pharmacokinetics associated with NuvaRing to existing scientific literature regarding hormonal contraceptives containing a third-generation progestin.

2. Analysis

Dr. Tischkau has a Ph.D. in physiology from the University of Illinois at Urbana-Champaign. (Doc. 1380, Exh. 4, at 1). She is an assistant professor in the Department of

Pharmacology at the Southern Illinois University School of Medicine, where she teaches a number of courses on pharmacology, including female reproductive pharmacology and principles of pharmacology. Dr. Tischkau is a member in several scientific societies, including the Society for the Study of Reproduction, Society for Neuroscience, Endocrine Society, Society of Toxicology, and the American Society for Pharmacology and Experimental Therapeutics. Dr. Tischkau serves as a reviewer for several academic publications, including *Pharmacology, Biochemistry & Behavior*, the *Journal of Neuroscience*, *Biology of Reproduction*, *Physiology & Behavior*, *Endocrinology*, and the *American Journal of Physiology*. As a published researcher, Dr. Tischkau has experience in combining knowledge gained from disparate scientific disciplines, including endocrinology, reproductive biology, pharmacology, and biochemistry.

Dr. Tischkau testified that she has expertise in reproductive endocrinology and reproductive pharmacology, including pharmacokinetics, a branch of pharmacology. (Doc. 1380, Exh. 5, "Tischkau Depo.," Nov. 3, 2011, at 89).

Organon contends that Dr. Tischkau, having admitted that she lacks expertise in hematology, VTE, and thrombosis, is not qualified to offer opinions touching upon on those subjects. However, Dr. Tischkau, through her academic training, research, and publication experience, is well-versed in analyzing scientific data and applying the results of other disciplines to her own work.

For the scope of her proposed testimony, Dr. Tischkau need not have expertise in VTEs, hematology, or thrombosis. She is not testifying on the accuracy of studies in those areas; rather, Dr. Tischkau is applying her own expertise in pharmacokinetics and pharmacodynamics to the results of other experts who are qualified in those fields. "[I]t is common in technical fields for an expert to base an opinion in part on what a different expert believes on the basis of expert

knowledge not possessed by the first expert . . . ." Dura Auto. Sys. of Ind., Inc. v. CTS Corp., 285 F.3d 609, 613 (7th Cir. 2002); see also Beck's Office Furniture & Supplies, Inc. v. Haworth, Inc., 94 F.3d 655 (10th Cir. 1996) (unpublished table decision). Considering her experience, I find that Dr. Tischkau is capable of understanding and applying the data underlying her opinion, including, *inter alia*, the NuvaRing clinical trials, studies on SHBG and APCr, and contraceptive cross-over studies. Dr. Tischkau may rely upon other experts' conclusions for the facts underlying her own expert opinion. Based on Dr. Tischkau's education and the knowledge and experience gained through her teaching and research, I find that she is qualified to testify as outlined above.

B. Reliability

In addition to the above-discussed qualifications, the following is pertinent to the reliability of Dr. Tischkau's opinions. In reaching her conclusions, Dr. Tischkau consulted the following:

- Studies, including studies and clinical trials sponsored or conducted by Organon, evaluating NuvaRing, its hormones and methods of delivery. (Doc. 1297, Exh. E).
- Relevant literature and data, including literature addressing SHBG, APCr, and EE in relation to hormonal contraceptives, coagulation, thromboembolism, and/or VTE risk. Id.
- Relevant epidemiological literature. Id.
- Relevant pharmacological literature. Id.

Organon argues that Dr. Tischkau's opinions are unreliable because portions of her expert report lack citations and closely track the language found in other academic literature. Although not disputing the substance of the material, Organon argues that this failure to appropriately cite sources renders Dr. Tischkau's opinions so incredible and reflects such an absence of scientific rigor that her methodology is itself suspect.

Credibility determinations are usually within the province of the fact-finder, however, a court may bar expert testimony where the credibility directly connects with the expert's methodology. See Elcock v. KMART Corp., 233 F.3d 734, 751 n.8 (3d Cir. 2000) (distinguishing between filing a fraudulent tax return and intentionally understating a scientific test's results); United States v. Herrera, 788 F. Supp. 2d 1026, 1029–35 (N.D. Cal. 2011) (finding expert unreliable who intentionally misrepresented study's conclusions). Although the failure to properly cite source material leaves Dr. Tischkau open to credibility attacks, the failure does not sufficiently impinge her methodology as to render it entirely unreliable. Dr. Tischkau's conclusions do not rely upon her having personally conducted the studies under scrutiny; rather, Dr. Tischkau conducted a review of the relevant literature. The failure to properly cite some material, the substance of which is not challenged, does not implicate methodology on the same level as discussed in the cases cited by defendants.[2]

Organon next argues that Dr. Tischkau's methodology is unreliable for failure to read additional underlying materials. Specifically, Organon alleges that Dr. Tischkau's opinion on the greater risk of thrombosis presented by third-generation progestins should be prohibited, because Dr. Tischkau improperly relied upon a review paper without thoroughly evaluating the sixteen studies analyzed therein. Organon alleges that some of the sixteen studies support their position that third-generation progestins do not present greater risk than second-generation progestins. The cases cited by Organon are easily distinguished from the present case. For example, in Weiner v. Snapple Bev. Corp., No. 08 Civ. 8742(DLC), 2010 U.S. Dist. LEXIS

[2] See, e.g., Abidishi v. Philip Morris, No. 98C1310, 1999 WL 756054 (N.D. Ill. Sept. 7, 1999) (finding expert's methodology unreliable where expert conducted no independent research, did not test the allegedly defective product and could not state whether crucial data came from animal studies or anecdotal reports); Herrera, 788 F. Supp. 2d at 1029–35 (finding unreliable expert who used "gimmick[s]" to "transform[] an accuracy rate of 61 out of 62 to less than one out of twenty").

79647 (S.D.N.Y. Aug. 3, 2010), the expert admitted to having reviewed *no* relevant literature. Likewise, the expert in Amorgianos had not read a single article when reaching his conclusion. Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 188–89 (E.D.N.Y. 2001). Finally, in Abdishi, the expert could not testify as to the origin, authorship, reliability, or authenticity of the "great majority" of documents upon which he relied. Abidishi, 1999 U.S. Dist. LEXIS 14903, at *16. Unlike those cases, here Dr. Tischkau reviewed a meta-analysis of the relevant literature, in addition to a number of other studies. Any weaknesses in the studies relied upon by Dr. Tischkau may be raised at trial.

Organon also alleges that Dr. Tischkau's report reflects such a level of carelessness that this Court should find it unreliable. Neither case Organon cites in support of this argument is analogous to the one here. In Solorio, the accident expert copied references from a previous expert report; however, the expert also reached his conclusions before conducting the necessary calculations, made calculations without performing prerequisite inspections, and referred to the plaintiff as being deceased even though she was still alive. Solorio v. Asplundh Tree Expert Co., No. 02 Civ. 8035(RJS), 2009 WL 755362, at *4 & n.9 (S.D.N.Y. Mar. 23, 2009). Likewise, in Lemmermann, the expert did not perform customary methods in diagnosing the plaintiff; rather, the expert reached a conclusion and then summarily diagnosed the plaintiff with a mutually exclusive condition when deposed. Lemmermann v. Blue Cross Blue Shield, 713 F. Supp. 2d 791, 809 n.21 (E.D. Wis. 2010). Dr. Tischkau does not exhibit the utter carelessness asserted by Defendants. I cannot conclude as a matter of law that her methodology is so unreliable as to disqualify Dr. Tischkau as an expert witness.

Organon finally argues that Dr. Tischkau's methodology is unreliable because she gave improper weight to studies and literature detrimental to Organon's position, relied on studies

tendered by Plaintiffs' counsel, and ignored data points integral to her conclusions. Organon's arguments related to Dr. Tischkau's reliance upon Plaintiffs' counsel, credibility allocations, and ignorance of data points address the weight of Dr. Tischkau's testimony, rather than admissibility of her conclusions. See Kuhn v. Wyeth, Inc., 686 F.3d 618, 628 (8th Cir. 2012) (finding assistance by plaintiff's counsel in writing expert report goes to credibility); id. at 633 (relegating allegations of "cherry picking" to cross-examination). As a result, they are more properly addressed during trial.

A jury may decide not to rely upon Dr. Tischkau's opinions, but I find that Dr. Tischkau's opinions are based on a reliable scientific methodology and sufficient foundation.

C. Assistance to the Trier of Fact

I find that Dr. Tischkau's opinions offer assistance to the trier of fact in its analysis of issues relevant to the dispute, as her testimony encompasses scientific opinions and observations not obvious to lay persons.

D. Specific Objections

Organon argues that Dr. Tischkau should not be permitted to testify that drugs containing second-generation progestins are safer than those containing third-generation progestins, which include NuvaRing, because Dr. Tischkau testified that she was not sure if androgenicity was the only reason to explain differences in risk between second- and third-generation progestins. However, Rule 702 does not require that an expert identify the precise causal mechanism for a given result. See Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1314 (9th Cir. 1995) ("Causation can be proved even when we don't know precisely how the damage occurred, if there is sufficiently compelling proof that the agent must have caused the damage somehow.").

Dr. Tischkau's methodology as to this statement consisted of a review of the relevant literature, including citations to a number of studies that concluded that progestins in third-generation contraceptives present a greater risk for thrombosis than do second-generation progestins. Dr. Tischkau also relied upon other experts' opinions that progestin counterbalances the blood-clotting effects of estrogen. Dr. Tischkau reviewed the pharmacological data for NuvaRing, which shows spikes in estrogen unaccompanied by similar spikes in progestin. From these inputs, Dr. Tischkau concluded that NuvaRing presents a greater risk for thrombosis than second-generation hormonal contraceptives. This methodology is sufficiently reliable for the purposes of Rule 702. Defendants will have the opportunity to cross-examine Dr. Tischkau on her conclusions as well as to present their own competing evidence.

Organon next argues that Dr. Tischkau should not be permitted to testify that "delivery of hormones vaginally causes increased variability" relative to other methods of delivery. I disagree. It is true that Dr. Tischkau was unable to reach an opinion on whether the vagina is "more or less stable an environment" for delivery of drugs than the gastro-intestinal (GI) system and that she did not have a "scientific opinion" on vaginal pH levels and their effect on the vaginal route of administration of drugs. However, I cannot say definitively whether those admissions foreclose Dr. Tischkau's conclusion. Dr. Tischkau based her opinion upon clinical studies that compared vaginally administered NuvaRing with oral contraception and contraception administered by skin patch. One such study indicated that there were larger variations in hormonal releases expected in vaginal rings than in oral tablets and showed "striking" inter-subject variability in EE profiles during ring use. Another study showed more relative inter-subject variability among ring users than in users of the patch or oral contraceptives. Based upon the record before me, I find that Dr. Tischkau's opinion regarding

the stability of vaginal administration versus oral administration of hormonal contraceptives to be adequately supported and to be admissible at trial.

Organon next argues that I should prohibit Dr. Tischkau's opinion that the "lack of androgenicity" in third-generation progestins "decrease[s] the ability of these compounds to counterbalance the effects of estrogens on production of clotting factors" because Dr. Tischkau cannot identify any data that support that opinion. However, Dr. Tischkau's expert report cites to several studies that support her opinion. See, e.g., (Doc. 1297, Exh. E) (listing Kemmeren, Increased Resistance of Activated Protein C in Women Taking Third-Generation Oral Contraceptives, *Blood Journal*, 2004 104: 1904–09). Defendants also argue that Dr. Tischkau should not be allowed to testify that elevated levels of estrogen are known to increase the risk of VTE. However, Organon's own experts have stated that it is understood in the scientific community that VTE risk is related to estrogen exposure. See, e.g., (Doc. 1370, Exh. 2, Declaration of David Grimes, at ¶ 30). I find that sufficient evidentiary support exists to allow this testimony by Dr. Tischkau.

Organon next alleges Dr. Tischkau's opinions that the variability in hormone concentrations exhibited by NuvaRing Clinical Trial No. 34218 subjects was "striking" or "significant" should be omitted,[3] because Dr. Tischkau did not evaluate clinical data for any other hormonal contraceptive. However, Organon fails to explain how the clinical data for other contraceptives is relevant to intra-study or intra-subject variability. Rather than addressing Dr.

[3] For example, Dr. Tischkau found that the amount of variability of serum EE in NuvaRing Clinical Trial 34218 was "significant." The time it took to reach a maximal serum concentration ("TMax") of EE ranged from 6 hours to 200 hours after insertion. (Tischkau Report, Doc. 1380, Exh. 2, at 13). Dr. Tischkau also found the secretion, absorption, and metabolism of EE to be widely variable among study participants because the standard deviation for Tmax was greater than the mean. (Tischkau Report at 16–17).

Tischkau's methodology, Defendants attack her conclusions. These disputes must resolve during cross examination. See Bonner v. ISP Technologies, Inc., 259 F.3d 924, 929–30 (8th Cir. 2001).

Finally, Organon argues that this Court should exclude Dr. Tischkau's opinion that the NuvaRing label was misleading due to incomplete or inaccurate n-values. However, Defendants again attack Dr. Tischkau's conclusion, rather than her methodology. Dr. Tischkau analyzed NuvaRing Clinical Trial No. 34218 and found that several data points were omitted in later reports. She compared the NuvaRing label to the data presented in Clinical Trial 34218 and determined that although the label stated that bioavailability data came from 16 subjects, the data for ENG came from 9 subjects and the data for EE came from 5 subjects. Nothing indicates that this methodology is deficient. Dr. Tischkau may present this opinion at trial.

IV. CONCLUSION

For the foregoing reasons, I find Dr. Tischkau qualified to opine as to the matters stated in her expert report as explained and clarified in Plaintiffs' responses to Organon's motion. Further, these opinions, as grounded in credible articles, studies, reports, and personal experience, are based on a reliable methodology.

Accordingly,

IT IS HEREBY ORDERED that Organon's motion to exclude the expert testimony of Dr. Tischkau (Doc. 1297) is **DENIED**.

RODNEY W. SIPPEL
UNITED STATES DISTRICT JUDGE

Dated this 4th day of March, 2013.